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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/611,835	07/07/2000	Brent R. Stockwell	50164/002002	6924

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EXAMINER	
FRIEND, TOMAS H F	

ART UNIT	PAPER NUMBER
1639	20

DATE MAILED: 05/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Applicati n N .	Applicant(s)	
	09/611,835	STOCKWELL ET AL.	
	Examin r	Art Unit	
	Tomas Friend	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *89-156* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *89-156* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☒ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Detailed Action

Change of Art Unit Designation

Please note: The Art Unit location of this application in the PTO has changed from Art Unit 1627 to Art Unit 1639. To aid in matching papers to this application, all further correspondence regarding this application should be directed to **Group Art Unit 1639**.

Status of the Application

A response to an office action including an amendment to the claims was received 08 November 2002 (Paper No. 14). A response to a notice of non-responsive amendment was received on 28 February 2003 (Paper No. 18).

Status of the Claims

Claims 1, 2, 5-12, 14-16, 18, 20-24, 28-33, 35, 37-44, 48, 49, 51, and 53-88 were examined on their merits in the most recent office action. In Paper No. 14, received 08 November 2002, applicants requested that the currently pending claims be replaced with new claims 89-156. The examiner interprets this request as a request to cancel claims 1-88 and add new claims 89-156. Claims 1-88 have been cancelled. Claims 89-156 are pending in the present application and examined in their merits.

The examiner thanks applicants' representative for pointing out that applicants' response in Paper No. 14 is responsive to the office action mailed 27 March 2002. The examiner regrets any inconvenience to applicants or applicants' representative.

The examiner wishes to thank Paul T. Clark for his helpfulness during the telephonic interviews on 08 and 29 April 2003.

Withdrawn Rejections/Objections

1. The objections to the specification over hyperlinks and trademarks are withdrawn in response to the entry of applicants' substitute specification.

2. All outstanding rejections under 35 U.S.C. 112, second paragraph, are withdrawn in response to applicants' cancellation of all pending claims.

3. The rejection of claims 1, 2, 11, 12, 14-16, 18, 20-24, 28-33, 35, 37-43, 48, 49, 51, 52-58, and 60-88 under 35 U.S.C. 103(a) as being unpatentable over Koller et al. Blood 86(5):1784-1793, is withdrawn in response to applicants' cancellation of the rejected claims.

Maintained Rejections

The statutory basis for each of the following rejections may be found in a prior office action.

Maintained Rejections – 35 U.S.C. 112, first paragraph

4. Claims 89-156 are rejected under 35 U.S.C. 112, first paragraph (written description), for reasons made of record in Paper No. 10 for claims 1, 2, 5-12, 14-16, 18, 20-24, 28-33, 35, 37-44, 48, 49, 51, and 53-88, now cancelled. The rejection of record is reproduced below for applicants' convenience.

Claims 1, 2, 5-12, 14-16, 18, 20-24, 28-33, 35, 37-44, 48, 49, 51, and 53-88 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed methods of screening two-compound or higher combinations for biological activity encompass any assay, any cell type, any biological activity, and any combination of any compounds or class of compounds. Consequently, applicants must show possession of representative examples that would indicate to one skilled in the relevant art that the inventor(s),

at the time the application was filed, had possession of methods that are representative of: [1] any assay, [2] any cell type, [3] any biological activity, and [4] any combination of any compounds or class of compounds. Simply providing exhaustive lists of potential compound classes based upon structure and/or function is not the same as demonstrating that applicants are in possession of methods that use any compounds. Similarly, simply listing numerous assay methods, cell types, and biological activities is not the same as demonstrating that applicants are in possession of methods that use any assay and any cell type to detect any biological activity.

Successfully screening for any synergistic (combination) biological activity using an array of any compounds, any cell type (including prokaryotic, plant, fungus, mammalian, reptilian, insect, etc.), and any assay without guidance as to the compounds to screens, assays to use, or biological activities screened for is unpredictable. Consequently, the importance of representative samples to demonstrate possession of the full scope of the claimed invention is high.

Applicants have exemplified methods which detect an anti-proliferative effect on human A549 lung carcinoma cells using a combinations of 7 FDA-approved drugs and an immunological assay. This example is not representative of the much broader scope of the claimed invention.

Applicants, in their response, consider the two different rejections over written description and scope of enablement together. The two separate rejections, however, address two different issues of patentability. In answering applicants' arguments, only arguments regarding the rejection being maintained are addressed.

Applicants argue that the law does not require that the specification demonstrate that numerous embodiments of the invention had been proven efficacious prior to the filing of the application.

Applicants' argument has been considered but it is not persuasive. The rejection of record makes no assertion that the law requires numerous embodiments or that they be proven efficacious prior to filing. The law requires that, at the time of filing, applicants are in possession of the claimed invention and that the invention be described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The presently claimed invention is directed to a method of discovering any combination of compounds having the ability to affect any biological property of any living cell in a way that is indicative of potential therapeutic efficacy in any animal. There are no limitations with regard to the numbers, structures, or functions of the combination of compounds, what the biological activity is or how it is affected, the cells used, the therapeutic activity indicated by the ability of the combination of the combination of compounds to affect the biological activity, or the animal in which the combination to be therapeutic. The cells used may be any single cell type in culture (prokaryotic or eukaryotic), any combinations of any cells in culture, or any cells within any living organism. Consequently, the scope of the claimed invention is enormously, broad.

The application as filed must reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the full scope of the claimed invention. Accordingly, one skilled in the art would seek to find in the specification, the description of an invention that can be used to discover any combination of compounds having the ability to affect any biological property of any living cell in a way that is indicative of potential therapeutic efficacy in any animal.

The specification as filed provides one example of a 7x7 array of compounds assayed using an immunoassay that may be indicative of antineoplastic activity based upon the ability of a combination of known drugs to inhibit proliferation of human lung cancer cells. In addition to the single working example, applicants provide lists of assays, test cells, and possible therapeutic efficacies. The claimed invention is not drawn to lists of compounds, assays, test cells, and possible therapeutic efficacies, however. The claimed invention is a method that requires the use of a set of compound combinations contacted with living test cells and measuring a (specific) biological property that is indicative of a (specific) therapeutic efficacy.

Applicants argue that it would be impossible to predict what combinations of compounds (if any) would provide indication of therapeutic efficacy. Given that one skilled in the art would have countless compound combinations from innumerable sources (included all plants, animals, fungi, and combinatorial chemical libraries including all possible sequences of amino acids, nucleic acids, and saccharides) as well as tens of thousands of assays and cells (including organisms), and thousands of therapeutic efficacies to choose from, the specification would not appear to indicate that applicants were in possession of the full scope of the claims at the time of

filing. Rather, it would appear that applicants were in possession of a method limited to the example in the specification and the concept to extrapolate these results to a universal scope.

5. Claims 89-156 are rejected under 35 U.S.C. 112, first paragraph (scope of enablement), for reasons made of record in Paper No. 10 for claims 1, 2, 5-12, 14-16, 18, 20-24, 28-33, 35, 37-44, 48, 49, 51, and 53-88, now cancelled. The rejection of record is reproduced below for applicants' convenience.

Claims 1, 2, 5-12, 14-16, 18, 20-24, 28-33, 35, 37-44, 48, 49, 51, and 53-88 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the assays and test compounds disclosed in the specification, does not reasonably provide enablement for any test compounds and any assay using any cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims without requiring undue experimentation.

Several factors are to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any required experimentation is "undue." These factors include:

1) the breadth of the claims
2) the nature of the invention
3) the state of the prior art
4) the level of one of ordinary skill
5) the level of predictability in the art
6) the amount of direction provided by the inventor
7) the existence of working examples
8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

See In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims encompass any compound including, but not limited to, nucleotides and nucleic acids, amino acids and peptides, lipids, glycolipids, sterols, prostaglandins, leukotrienes, proteins, glycoproteins, proteoglycans, glucosaminoglycans, coenzymes, glycerophospholipids, saccharides, polysaccharides, aminoglycosides, peptidomimetics, and fatty acids.

The invention is a method that involves screening combinations of compounds for unexpected results (e.g. synergistic action of two compounds not expected to produce a synergistic action).

Screening of particular classes of compounds for specific biological functions was known in the art. The prior art provides large numbers of cell-based assays for large variety of functional screens for many classes of compounds. Assays were performed on individual compounds or groups of structurally or functionally related compounds that one of ordinary skill in the art would suspect to be active in the screening assay. The compounds screened were not "random" in the sense that there would be no reason to expect them to show activity in the assay being used.

The level of predictability in the art for screening depended on the quality and amount of information used to select test compounds for a particular screen. Screening combinations of compounds that were known to show activity in an assay for synergistic effects was predictable. Many synergistic drug combinations were known in the art. The predictability of screening compounds randomly (i.e. without any structural or functional basis to predict activity in an assay) for synergy was very low. A result showing cooperativity (or synergy) between <u>any</u> two compounds in a cell-based assay without any prior data on structural-function relationships would have been considered "unexpected."

The inventors provide general guidance with respect to a strategy for screening large numbers of compounds for synergistic activity as well as a specific example in which the invention has been reduced to practice. Guidance is lacking, however, with respect to the selection of compounds to be tested for any particular assay. The success of the method would appear to depend upon the ability of one using the invention to select compounds that would include combinations that display synergistic activity. The ability to screen even very large numbers of unnamed compounds (i.e. randomly selected compounds) for an unspecified activity does not overcome the lack of guidance with respect to compound selection for a specific assay.

One of ordinary skill in the art using the claimed method would be "fishing" for an undisclosed activity displayed by a combination of compounds using an unspecified assay. Because no relationship between compounds to be screened or between compounds to be screened and the activity screened for is provided, one of ordinary skill in the art would be

required to conduct research to determine the required relationships needed to increase the likelihood of positive results or to rely on searching enormous numbers of compounds without any reasonable expectation that a positive result would be achieved.

Applicants argue that even though the results for any given combination of compounds is highly unpredictable (impossible) the methods used to produce the unexpected results are set out in such detail that the disclosure is, nevertheless, enabling. Applicants also argue that the experimentation required to screen random libraries of compounds is not undue because automated screening methods can screen very large numbers of compounds.

Applicants' arguments have been fully considered but they are not persuasive. Applicants have shown that a 7x7 array of known drugs can be screened for a combination that inhibits cell proliferation. Applicants indicate that this result is unexpected. Applicants have provided lists of other cells and assays that might be used with the claimed method and appear to indicate that the structures of the compounds used in the method are not critical. It is not clear that an unexpected result in a single assay with 49 combinations of seven known drugs enables the claimed method commensurate in scope with the claims, which encompasses literally all compounds, innumerable combinations of 2 or more of these compounds, at least tens of thousands of cell types and assays, and thousands of therapeutic efficacies. Applicants assert that no initial "selection" of compounds to be used is required. Applicants have not demonstrated or disclosed a single specific embodiment of the invention which uses extracts from plants or animals, for example, other than to list extracts as possible sources of compounds. The only fully described embodiment of the claimed method uses only well characterized FDA approved drug compounds with known physical, chemical, and pharmacological properties at known concentrations. The compounds are pure and have been tested for optimal dose ranges for their respective efficacies. One skilled in the art wishing to use uncharacterized extracts or uncharacterized compounds from a synthetic chemical library may not know the concentrations of the compounds used, for example, or how the compounds would react to each other and any components of a cell culture or animal system. One skilled in the art using the invention would not, according to the specification and applicants' arguments, use any theoretical criteria such as concentration, solubility, chemical reactivity, efficacy with a different disease, or FDA approval to select compounds to be used.

With regard to applicants' arguments that automated screening enables the claimed method because of the volume of compound combinations that can be screened in a day, for example, it is noted that the methods of claims 89, 135, and 154 encompass as few as 49 combinations of seven compounds, the method of claim 114 encompass as few as 200 combinations of 7 different compounds, and the method of claim 149 encompasses as few as 10,000 unique combinations of 7 different compounds. Consequently, the reliance on the "brut force" approach to enable the claimed methods is not persuasive.

Applicants argue that the claimed method has been carried out more than a million times since the filing of this application using a variety of cell types. This argument is not persuasive because the uses of the claimed method to which applicants refer are not of record in the application and the examiner has no means of assessing their relevance to the present application.

New Grounds of Rejection

The statutory basis for each of the following rejections not found below may be found in a prior office action.

New Grounds of Rejection – 35 U.S.C. 112, first paragraph

6. Claims 89-153 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention (new matter). The newly added claims recite that the effect of the combination of compounds on the biological property of the test cells is "*qualitatively or quantitatively superior to the effect of each compound, individually, on said biological property of the test cells.*" The disclosure does not appear to support the introduction of this claim limitation. Applicants have not indicated where support for this limitation can be found in the application as filed. In accordance with MPEP 714.02, applicant should specifically point out where support can be found for any amendment made to the disclosure.

New Grounds of Rejection – 35 U.S.C. 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 149-153 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is not clear how one can generate 10,000 different unique combinations of 7 different compounds. Accordingly, one skilled in the art would not know how to interpret this limitation.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Tomas Friend** at telephone number **(703) 308-4548**. The examiner's normal schedule is four, ten-hour days per week including Saturdays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (703) 306-3217. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-2742.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist at (703) 308-1235.

Tomas Friend, Ph.D.
16 May 2003

ANDREW WANG
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600